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Extravascular lung water index and global end-diastolic volume index should be corrected in children

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Abstract

Purpose: The aim of the present study was to explain why extravascular lung water index (EVLWI) is higher and why global end-diastolic blood volume index (GEDVI) is lower in young children when measured with the PiCCO system (Pulsion, Munich, Germany).

Materials and Methods: We pooled available data from literature from children concerning organ weight derived from autopsy studies and computed tomographic lung measurements. These data include age, height, body weight, body surface area (BSA), and lung and heart weights. For standard, age-dependent weight and height, we used published data from the World Health Organization. From the available data, we calculated the lung weight–to–body weight ratio, the heart weight–to–BSA ratio, and the end-diastolic volume–to–BSA ratio. We compared these ratios to body growth and development.

Results: Lung weight develops more slowly and with less magnitude than does body weight. In addition, the (relatively) greater lung weight in younger children results in a higher amount of pulmonary blood volume. This explains the higher EVLWI in young children. End-diastolic blood volume and heart weight increase faster and are more pronounced compared with BSA. This explains the lower GEDVI in young children. We propose correction factors for comparing EVLWI and GEDVI with adult reference values.

Conclusions: Extravascular lung water index is higher and GEDVI is lower in young children because of changing organ-to-body weight relationships during growth.

1. Introduction

Extravascular lung water (EVLW) is the amount of fluid present in the extravascular lung space [1,2]. Extravascular lung water can be measured at the bedside using the single-indicator transpulmonary thermodilution (TPTD) technique and quantifies the amount of pulmonary edema [3]. Measurement of EVLW requires a femoral artery catheter equipped with a thermistor, the injection of ice-cold saline through a central venous catheter, and a special monitoring device PiCCo; Pulsion, Munich, Germany). Besides EVLW, the TPTD technique also measures global end-diastolic volume (GEDV) and cardiac output (CO) [4-6]. Global end-diastolic volume reflects cardiac preload in adults and children [4,7].

To compare subjects of different sizes, variables such as lung water or CO are indexed to body dimensions. This is based on the assumption that the relation between the variable and the body dimension used for indexing is linear.

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Traditionally, EVLW is indexed (EVLWI) to actual body weight, whereas GEDV and CO are indexed using body surface area (BSA) calculated from body height and weight (GEDVI and Cardiac Index, respectively).

The PiCCO device measures CO reliably in children [6,8]. However, EVLWI in young children seems to be much higher compared with those of adult values; therefore, its validity and use in children are questioned [5,7,9-11]. In contrast to EVLWI, GEDVI is lower in young children [5,7]. Up to now, no explanation for these deviant values in young children has been given. As a result, there are still no reference values available for infants and preschool children.

This study aimed to find an explanation for higher EVLWI and lower GEDVI values in young children. We therefore studied existing data available in the literature concerning lung development, lung weight, lung growth, and the dimensional development of heart and body in children and adults. Subsequently, we propose age- and weight-dependent pediatric "correction factors."

2. Methods

Basic age-weight and age-height relations were collected from a data set provided by the World Health Organization (WHO) [12,13]. These data were derived from children raised in different continents in an environment that minimized constraints to growth such as poor diet, passive smoking, and repeated infections. Therefore, these standards may depict the global average normal human growth and reflect average ideal pediatric body proportions. We averaged the WHO data for boys and girls and considered weight for age provided by the WHO as ideal and equal to predicted body weight (PBW). We calculated BSA from weight and height using the algorithm described by Haycock et al [14].

Next, we pooled available data concerning lung weight in relation to age derived from autopsy studies and computed tomographic lung measurements in children [15-18]. Lung water measurement using the PiCCO system requires the use of a 3F arterial femoral catheter. Because this is only used in children weighing more than 3.5 kg, we excluded data from smaller or preterm children. We divided lung weight by body weight to calculate the lung weight–to–body weight ratio using the body weight presented in the available data. In 2 studies, body weight was not provided [17,18]. In these cases, we used the WHO data to determine body weight from age. Subsequently, we pooled data from several adult autopsy studies to gain insight into the relation between lung and body weights in adults [19-25].

We also pooled available data concerning heart weight in relation to age derived from autopsy studies in children [15,16,18,26]. For calculating the heart weight–to–BSA ratio, we determined BSA using the weight and height provided by the WHO data set for the given age.

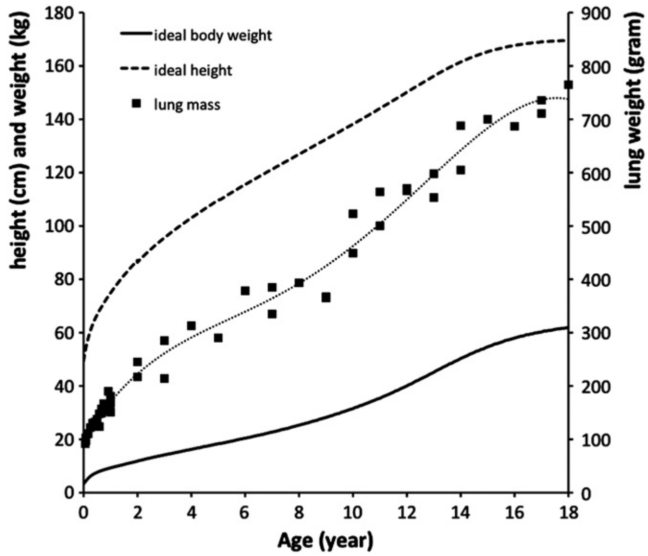

Fig. 1 The relation between ideal body weight, ideal height, and lung weight with age. Ideal body weight and ideal height in relation to age are based on the WHO data [12]. Height and weight are mean values for boys and girls. Lung weight represents pooled data [15-18]. The dotted line represents the best-fit curve. Lung weight (g) = $-0.0311x^4 + 1.1257x^3 - 12.857x^2 + 83.453x + 98.605$. $r^2 = 0.99$, with x = age in years.

Finally, correction factors were designed. Because this was not the primary goal of this study, this part is described in Appendix 2.

Best-fit analyses were performed using Excel 2008 for Mac (Microsoft, Redmond, WA, USA).

3. Results

The relation of age with ideal body weight and ideal height is presented in Fig. 1, together with the pooled data

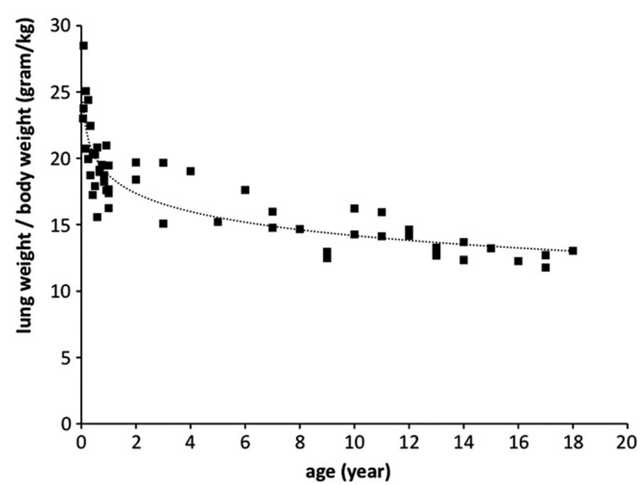

Fig. 2 The lung weight–to–body weight ratio related to age. Lung weight represents pooled data [15-18]. The dotted line reflects the best-fit curve. Lung weight/body weight (g/kg) = $-1.982\ln(x) + 18.728$. $r^2 = 0.78$, with x = age in years.

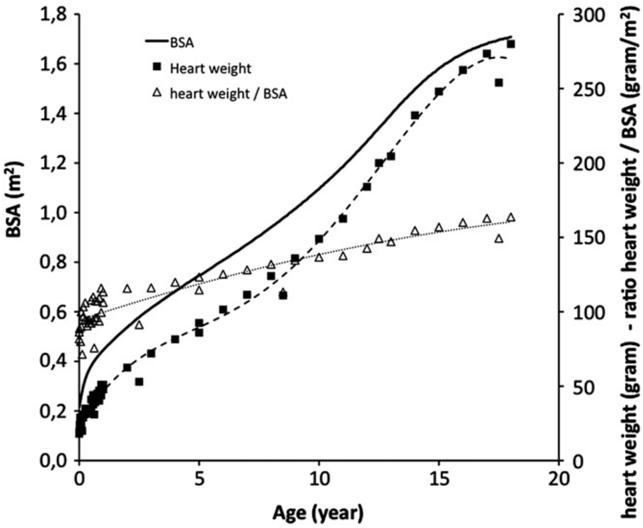

Fig. 3 The relation between BSA, heart weight, and the heart weight–to–BSA ratio with age. Body surface area in relation to age is based on the WHO data [12]. Body surface area represents mean values for boys and girls. Heart weight represents pooled data [15,16,18,26]. The best-fit for heart weight to age: heart weight (g) = $-0.0135x^4 + 0.4711x^3 - 4.8579x^2 + 27.426x + 23.485$. $r^2 = 0.995$, with x = age in years. The best-fit for heart weight to BSA: ratio (g/m^2) = $-0.0918x^2 + 5.3222x + 94.381$. $r^2 = 0.86$, with x = age in years.

from lung weight in children. Fig. 2 presents the relation between age and the ratio of lung weight to body weight. The ratio is between 16 and 28 g/kg at 1 month and reaches 11 to 13 g/kg at 18 years. Fig. 3 shows the relation of BSA to age together with the pooled data of heart weight. The ratio of heart weight to BSA is also depicted in Fig. 3. At last, we designed pediatric correction factors for EVLWI and GEDVI (Appendix 2).

4. Discussion

We show, based on existing data, that the lung weight–to–body weight ratio declines with age (Fig. 2). The fastest decline occurs within the first years of life. Because lung water is strongly related to lung weight and is, at the same time, indexed to body weight, these results offer an explanation why EVLWI is higher in young children compared with that of older children or adults.

Extravascular lung water is the amount of fluid that is present in the extravascular space of the lung [1,2]. The quantity of extravascular fluid is dependent on the net driving force over the vessel wall and will be proportional to tissue mass. Therefore, when perfusion is equally distributed, an increase in organ tissue mass will lead to a similar increase in the quantity of extravascular fluid. A higher absolute value of EVLW in young children is not in conjunction with these physiologic rules. At present, there is one animal study comparing data of healthy newborn lambs to that of adult sheep [27]. In this study, lung water was determined using the gravimetric technology. The study shows that the lung weight–to–body weight ratio is 24.3 g/kg in newborn lambs and 12.9 g/kg in adult sheep. This seems to be similar to humans because lung weight–to–body weight ratio in adults is roughly between 12 and 17 g/kg, with a mean around 14 g/kg [19,21,22,24,25]. The amount of EVLWI was 13.3 mL/kg in lamb and 6.1 mL/kg in sheep. Most importantly, the lung water–to–dry lung weight ratio was 4.0 mL/g in both lambs and sheep [27]. Snapper et al [28] measured lung water in sheep while decreasing the lung weight by tying off parts of the lung. Their results show that there is a linear relation between dry lung weight and lung water, with an r^2 of 0.95. From these studies, it can be concluded that lung water is indeed a proportional fraction of the tissue mass. At the same time, it can be concluded that lung weight can be used to study the potential quantity of lung water.

The total weight of newborn human lungs is approximately 100 g at 1 month, whereas the weight of adult lungs is approximately 1000 g [22]. The relation between lung weight and age is depicted in Fig. 1. Until the age of 8 years, there is more tissue-to-air compared with older children and adults, and the fastest change occurs in the first 2 years [29,30]. There is approximately a 2.5-fold increase in the tissue-to-air ratio from the newborn to children at the age of 6 years. Up to the age of 2 years, the growth of lung volume is probably related to both an increase in the number and size of alveoli [17,29,31]. The development of height and especially body weight is rapid in the first year of life, but body weight increases more rapidly and with greater magnitude than height (Fig. 1). Although both body and lung weights develop rapidly in young children, body weight increases even faster, and thus, the lung weight–to–body weight ratio decreases by a factor of approximately 0.5 during childhood and adolescence human development (Fig. 2) [15,32]. This implies that young children have relatively more lung tissue mass in relation to body weight compared with older children or adults. Because a higher lung tissue mass is related to a larger EVLW volume, this offers an explanation why young children have a higher EVLWI (up to 100%) compared with older children or adults.

The higher lung tissue mass in children also has consequences regarding the calculation of EVLW itself. Appendix 1 shows the normal calculation of EVLW and GEDV using the TPTD technique. Because all TPTD measurements are based on physical properties, they are probably reliable in all subjects. However, for the calculation of EVLW, a factor of 1.25 between GEDV and intrathoracic blood volume (ITBV) is used [33]. This factor represents the relation between pulmonary blood volume (PBV) and GEDV and thereby assumes a constant and linear relation. However, it has been shown that this factor is not equal in all subjects [3]. Moreover, with the relatively larger lung weight in young children, as shown above, the PBV will also be larger. When a falsely low factor is used, ITBV will be too low, and as a result, EVLW will be too high (Appendix 1). We showed in an earlier pediatric study that this factor is indeed weight- (and age-) dependent and varies between approximately 1.5 in young children and 1.2 in older children [9]. This phenomenon offers an additional explanation why EVLWI is higher in younger children, although the effect is much smaller.

In contrast to EVLW, GEDV is a virtual volume including the end-diastolic volumes of left and right atria and ventricles plus the volume of central veins and aorta between the point of injection and the point of detection of the indicator. Therefore, GEDV has no anatomical counterpart that can be used for indexing. Apart from heart weight (Fig. 3), the development of end-diastolic blood volume (EDV) measured using angiography or echocardiography will closely resemble GEDV. During growth, EDV, measured using angiography, increased from 25 mL with a BSA of 0.5 m^2 to 125 mL at 1.5 m^2 [34]. Therefore, EDV increased with a factor of 5 and BSA with a factor of 3. There was an exponential relation between development of EDV and BSA [34]. This exponential relation was confirmed by Buechel et al [35] using cardiac magnetic resonance imaging data. Using 3-dimensional echocardiography, Poutanen and Jokinen [36] showed that left ventricular mass–to–BSA ratio increased from 50 g/m^2 at 3 years to 80 g/m^2 at 17 years. During human development, left ventricular mass increased with a factor of 4 (from 35 to 130 g), whereas BSA increased with a factor of 2.5 (from 0.7 to 1.7) in healthy humans ranging from 2 to 27 years old [36]. The available data, shown in Fig. 3, and the aforementioned data from EDV in relation to age offer an explanation why younger children have a lower GEDVI compared with older children or adults.

Extravascular lung water and GEDV need to be indexed to enable a comparison between individuals of different sizes and to use normal values. Otherwise, the measurements have less clinical value. However, because of the nonlinear relation between lung and body weights, it could be argued that lung water should be indexed to other body dimensions (such as height). Actually, lung water should be indexed to lung weight itself, but this seems impossible because lung weight cannot be measured in vivo and because no body variable develops linearly with lung weight [27]. Likewise, GEDV should be indexed to a more comparable body dimension instead of BSA, but this is even more difficult than for EVLW. Therefore, we propose to continue to index lung water to body weight and GEDV to BSA. In doing so, one may choose between accepting higher values of EVLWI and lower values of GEDVI in young children and develop age-dependent normal values or implement a correction factor for correcting or "normalizing" values of children. In Appendix 2, we propose the development of correction factors to acquire comparable EVLWI and GEDVI values in all ages.

The results of this study apply to all children monitored using the PiCCO system. However, there are some limitations. All data are based on existing studies that were not designed to specifically study higher EVLWI and lower GEDVI values in young children. In addition, the autopsy data might not always refer to healthy lung or heart samples and might therefore not always reflect standard values. This might be an explanation for the scatter of data of the lung weight–to–body weight ratio, resulting in a less optimal r^2 of 0.78. In addition, age might be less suitable for a correction of lung water and GEDV; instead, height could be more suitable. On the other hand, autopsy data on lung weight are almost all related to body weight or age, and height is often not provided.

In summary, we offer, for the first time, an explanation for higher values of EVLWI and lower values of GEDVI in young children. They are caused by age-related changes in the ratio of lung weight to body weight and in the ratio of EDV and heart weight to BSA during growth. In addition, in young children, the PBV seems larger compared with GEDV. We propose a correction algorithm for adjusting EVLWI and GEDVI to adult reference values. The advantage is that these measurements can now be interpreted in relation to known normal values. On the other hand, every calculation or correction factor adds a source of error. Therefore, more research is necessary to confirm the utility of the proposed algorithms. Caution must still be applied when interpreting EVLWI and GEDVI (corrected or not) in the clinical setting in small children.

Appendix 1. Calculation of EVLW and GEDV

The TPTD technique delivers 3 basic measurements:

1. Cardiac output (L/min)
2. Mean transit time (MTt) (s)
3. Mean downslope time (DSt) (s)

Secondary required parameters include the following:

1. Body weight (kg)
2. Height (cm)
3. Body surface area based on weight and height is calculated by a specific formula [14]

Calculations by the PiCCO device are as follows:

A. Intrathoracic thermal volume (ITTV) = CO × MTt × 1000/60 (mL)
B. Pulmonary thermal volume (PTV) = CO × DSt × 1000/60 (mL)
C. GEDV = ITTV − PTV (mL)
D. ITBV = GEDV × 1.25
E. EVLW = ITTV − ITBV (mL)
F. EVLWI = EVLW/body weight (mL/kg)
G. GEDVI = GEDV/BSA (mL/m^2)

Important issues

The calculation of ITBV using the assumed factor of 1.25 (calculation D) is based on one study in adult subjects [33]. The factor can be different between individuals but can also be different related to age [3,15].

The premise that PTV can be calculated from the DSt is that this must be the largest "mixing chamber" of blood and indicator. The PBV must therefore be larger than GEDV.

Appendix 2. Pediatric correction and indexing of EVLW and GEDV

Pediatric correction of EVLWI

Starting point

Although pediatric data are lacking to prevent obese children from having a false low EVLWI, it seems practical to use Predicted Body Weight (PBW) in children [37-39]. PBW might best be calculated from height because predicted weight is more closely related to height [12].

Step 1

The relation between GEDV and ITBV is reflected by a factor of 1.25 (Appendix 1, formula D). However, in children, this factor is approximately 1.50 at 3.5 kg body weight and declines to 1.25 at a body weight of 25 kg [9]. The fastest decrease occurs during the first 2 years of life. Because the correlation between this factor and body weight appeared to be the strongest, we used body weight instead of age [9]. Because the relation between lung and body weights is logarithmic (Fig. 2), a similar type of algorithm should be used. Therefore, we propose to calculate ITBV in children as follows:

$$\text{ITBV pediatric } (\text{ITBV}_\text{P}) = (-0.1 * \ln(x) + 1.6128) \times \text{ GEDV with } [x = \text{body weight in kg}]$$

Step 2

The last correction should compensate for the changing lung weight–to–body weight ratio. The correction factor for the change in lung weight–to–body weight ratio is based on the logarithmic best-fit curve shown in Fig. 2. A ratio of 12 g/kg lung weight to body weight serves as the "end" value at the age of 18 years and a ratio of 23 as a starting value. Furthermore, the "elbow" in the curve is positioned at the age of 2 years. We propose to calculate EVLWI as follows:

$$\text{EVLWI pediatric } (\text{EVLWI}_\text{P}) = \text{EVLWI } *(-0.088*\ln(x) + 0.7133) \text{ with } [x = \text{age in years}]$$

Pediatric correction of GEDVI

Starting point

BSA should be calculated using PBW such as in EVLW.

Step 1

The correction factor for adapting the relation between cardiac dimensions and BSA was developed as follows: the algorithm is based on the best-fit curve shown in Fig. 3. The correction factor is 1 at the age of 18 years and 2 at the age of 1 month. Again, the elbow in the curve is positioned at the age of 2 years. It corrects the calculated GEDVI. We propose to calculate ITBV in children as follows:

$$\text{GEDVI pediatric } (\text{GEDVI}_\text{P}) = \text{GEDVI } * 1.4188x^{-0.125} [x = \text{age in years}]$$

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